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Green Solvents in Synthesis of Schiff's Base: A Comprehensive Review of Sustainable Approach

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Abstract

The synthesis of Schiff's bases is a fundamental process of organic synthesis that traditionally involves using hazardous organic solvents. These solvents pose significant risks to both the environment and human health due to their toxicity, volatility, and persistence in nature. These negative effects of organic solvents have led to the development of greener and mores ustainable alternatives that aligns with the principles of Green Chemistry. This review paper aims to provide a comprehensive overview of the effectiveness of various green solvents such as water, ionic liquids and supercritical carbon dioxide, in promoting the condensation reaction between amines and aldehyde or ketones. It first discusses about the various traditional solvents used in synthesis of Schiff's bases and their advantages and disadvantages. The paper then discuss about advantages, disadvantages and the challenges associated with the use of water, Ionic liquids and supercritical carbon dioxide, as solvent in Schiff's base synthesis. Water, is highlighted for its non-toxic, non-flammable, and environmentally benign properties, leading to high yields of Schiff's bases without the need for additional catalysts, as reported in number of research studies .Ionic liquids, characterized by their low volatility and tunable properties, are explored as versatile green solvents. Supercritical carbon dioxide (scCO 2) is presented as another promising green solvent since it is non-toxic, non-flammable, and can be easily removed from the reaction mixture by depressurization, leaving no solvent residues. Furthermore, these solvents can be designed to possess specific characteristics that enhance the reaction efficiency and selectivity. Additionally ,this review highlights the importance of considering green chemistry principles in the synthesis of Schiff's bases and emphasizes the potential of green solvents to revolutionize this field.

Keywords: Schiff's base, green solvents, ionic liquids, supercritical carbon dioxide, sustainable synthesis

INTRODUCTION

Background and Significance of Schiff's Base

Schiff's bases, named after the German chemist Hugo Schiff [1-3]. are versatile organic compounds, derived from the condensation reaction between a primary amine and an aldehyde or ketone [4]. These compounds are characterized by an azomethine or imine (>C= N) functional group and possess a wide range of chemical and biological activities. Schiff bases, due to electron-donating nitrogen in their structure can act as versatile ligands and can form complexes with nearly all metals. These complexes are studied for their catalytic, magnetic, and optical properties and are used as sensors, catalysts, and medicinal chemistry for their antimicrobial and antitumor activities. The interesting application of Schiff bases in analytical, biological, and medicinal, fields underlines their importance as complexation agents. These metal complexes of Schiff bases exhibit a broad spectrum of biological activities [5,6]. making them significant in therapeutic

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applications. They have been found to possess antimicrobial, urease inhibitory, anti-inflammatory, anti-ulcerogenic, antioxidant, pesticidal, cytotoxic, and anticancer properties. Furthermore, Schiff bases and their complexes exhibit high thermal stability, making them useful as catalysts in reactions at high temperatures. Their ability to undergo quantitative exchange reactions with various amines, aldehydes, and acetals showcases their versatility and potential for generating new compounds through amine exchange processes, further expanding their applicability in synthetic and industrial chemistry. Several research studies have highlighted the role of Schiff bases in catalysis [7-14]. and medicinal chemistry [15-20]. Additionally, Schiff bases have also been reported as selective and efficient sensing materials in optical, electrochemical, and membrane sensors.

These compounds have been the subject of extensive research due to their wide range of applications in various fields of science and industry. The versatility of Schiff bases is attributed to their straightforward synthesis, which allows for the joining of different structural features, enhancing flexibility through the -C=N- part. Schiff's bases are typically synthesized through the refluxing of an amine and aldehyde in an organic solvent. There are variations in the preparation method, such as conducting the reaction at room temperature, refluxing the mixture in heptane with the presence of acetic acid, or employing a Dean-Stark apparatus to azeotropically remove water using benzene and acid. It is often necessary to shift the equilibrium of the reaction by removing water, which can be achieved through distillation using an azeotropic process or by utilizing appropriate drying agents. FIG 1

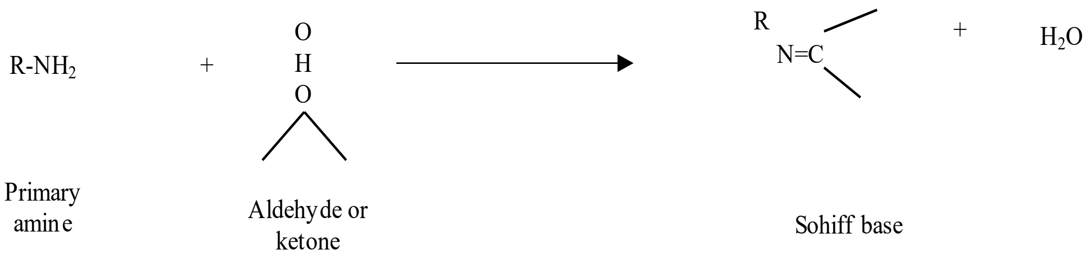


Figure 1. Schiff base synthesis equation.

Challenges In Traditional Synthesis of Schiff's Bases

The synthesis of Schiff's bases has traditionally involved the use of conventional solvents such as benzene, DMF, DMSO, heptane, ethanol, methanol, and toluene. When selecting a solvent for Schiff base synthesis we consider factors such as the reaction conditions, environmental impact, cost, and safety. The studies mentioned in the literature suggest the versatility and range of options available, with each having its unique advantages depending on the specific requirements of the synthesis. The choice of solvent is critical not just for reaction efficiency but also for the purification process. Solvents like water and alcohols are preferred for their green chemistry aspects, while DMSO and DMF are chosen for their solubilizing power and high boiling points, useful in reactions requiring heat. The different types of solvents used in Schiff base synthesis along with their properties, advantages, and disadvantages are tabulated in Table 1.

Table 1. Commonly used Conventional solvents in Schiff base synthesis.

Name of Solvents	Properties	Advantages	Disadvantages	References
Benzene and Toluene	-Non-polar,-relatively high boiling points.	Good for non-polar conditions,-excellent solvents for many organic compounds.-toluene suitable for hydrophobic substrates-Can be used for conducting reactions at elevated temperatures without significant evaporation.	Toxic, especially benzene- a known carcinogen; -flammable.	[21][22][23]

DMF	Aprotic Polar solvent Hight boiling Point	Can dissolve many polar and non-polar compounds	VOC, not environmenta friendly Expensive Difficult to recover	[24]
DMSO	Aprotic solvent, Highly polar,-High boiling point,	-Can dissolve many polar and non-polar compounds, -useful in various reactions.	Can be absorbed through the skin, potentially causing health issues; -difficult to remove due to high boiling point.	[25]
Alcohols(Methanol and Ethanol)	Polar solvents, moderate boiling points.	Relatively green (especially ethanol), good for reactions requiring polar conditions.	Flammable, moderate toxicity, methanol is particularly toxic.	[26], [27], [28], [29]

As clear from Table 1, the synthesis of Schiff bases through conventional methods in traditional solvents presents several challenges that pose environmental, economic, and efficiency concerns.

- *Environmental concerns:* One of the significant challenges in the conventional synthesis of Schiff bases involves the use of organic solvents, which are often volatile, toxic, and non-biodegradable. These solvents contribute to environmental pollution and pose health risks to researchers. The need for large volumes of these solvents further exacerbates their environmental impact, making the process less sustainable and eco-friendly.
- *Reaction efficiency and selectivity*: Conventional methods sometimes suffer from low reaction efficiency and selectivity. The formation of Schiff bases can be accompanied by side reactions, including polymerization of the imine product, which complicates the purification process and reduces the overall yield. Achieving high selectivity is crucial when synthesizing Schiff bases with specific desired properties, especially in the development of pharmaceuticals and advanced materials.
- *Thermal stability and harsh reaction conditions*: Many Schiff base syntheses require elevated temperatures to proceed at a reasonable rate. However, this can be problematic for substrates sensitive to heat, leading to degradation or unwanted side reactions. Moreover, harsh reaction conditions, including the use of strong acids or bases as catalysts, can limit the functional group compatibility, restricting the range of substrates that can be used.
- *Scale-up issues*: Scaling up the synthesis of Schiff bases is often challenging due to the precise control required over reaction conditions. The sensitivity of imine formation to moisture and the need for anhydrous conditions or inert atmospheres can be particularly problematic in larger-scale reactions. Additionally, the removal of solvents and purification of the product can become more difficult and less efficient as the reaction scale increases.

Addressing these challenges is crucial for advancing the synthesis of Schiff bases and expanding their applications. Innovations such as the use of green solvents, solvent-free conditions, microwave-assisted synthesis, or the development of more selective catalysts and reaction conditions have shown promise in mitigating some of the environmental and efficiency-related issues. Furthermore, exploring alternative synthetic routes involving green solvents that bypass some of the conventional method limitations could provide more sustainable and efficient approaches to Schiff base production.

GREEN SOLVENTS AS A SUITABLE ALTERNATIVE

Most of the conventional solvents like benzene, toluene, DMF, DMSO, etc., which are used in Schiff base synthesis are often toxic, flammable, and non-biodegradable, posing significant risks to human health [30, 31]. and detrimental impact on environments like VOCs, depletion of ozone layer, soil contamination, and water pollution. The disadvantages of these solvents are presented in Figure (2). Due to the disadvantages of conventional solvents as depicted here, there has been a significant focus, both in academic research and the chemical industry, on the advancement of environmentally friendly solvents and reaction conditions. The quest for more sustainable and environmentally benign synthetic routes in organic chemistry has led to the exploration of green solvents as alternatives to traditional volatile organic compounds (VOCs).

The. green synthesis of Schiff bases using environmentally benign solvents and techniques presents a promising approach to organic synthesis. These methods not only align with the principles of green chemistry by reducing toxic waste and energy consumption but also offer operational advantages in terms of yield and reaction efficiency. The transition towards greener alternatives in the synthesis of Schiff bases is an essential step forward in sustainable chemistry. There are several studies reported in the recent past based on greener alternatives[32]. The synthesis of Schiff bases using green solvents is a significant area of research aimed at developing eco-friendly and efficient synthetic pathways

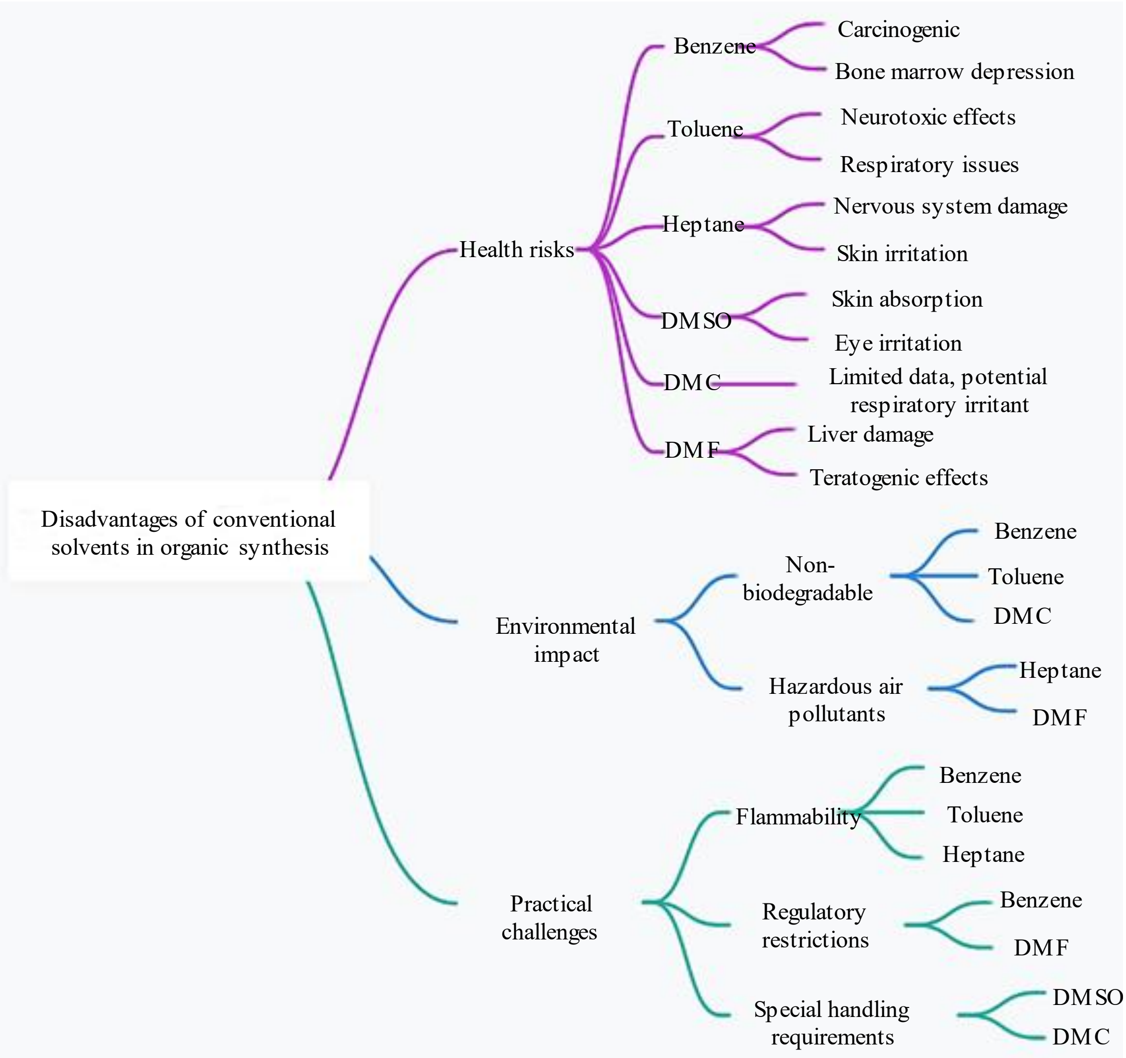


Figure 2. Disadvantages of using conventional solvents.

GREEN SOLVENTS IN THE SYNTHESIS OF SCHIFF'S BASE

Green solvents include water, ionic liquids, supercritical fluids, deep eutectic solvents, and bio-based solvents, among others. These solvents possess favourable properties such as low toxicity, non-flammability, low vapor pressure, and high solubility for a wide range of substrates. By employing green solvents, we can not only enhance the safety and sustainability of Schiff's base synthesis but also improve the reaction efficiency and product yield. The use of green solvents aligns with the principles of green chemistry, which aims to design chemical processes that are efficient, cost-effective, and environmentally benign. We aim to explore the sustainable synthesis of Schiff's bases using green solvents in this paper. The use of green solvents in the synthesis of Schiff bases has gained significant attention for its environmental and economic benefits over traditional methods. Several recent research studies have reported the use of green solvents such as water, ionic liquids, supercritical carbon dioxide, and ethanol as efficient and environmentally friendly solvents for organic synthesis

Water as Green Solvent

Water is a green solvent with the advantages of being non-toxic, inexpensive, and environmentally benign. Some Schiff base reactions can occur in water without the need for catalysts. Tanaka and Shiraishi devised a streamlined and eco-friendly method for synthesizing various imines, leveraging water as the solvent in a room-temperature suspension approach. This innovative technique circumvents the need for catalysts, avoids the use of excessive aromatic solvents, and eliminates the need for water removal through azeotropic techniques [33]. Characterized by rapid reaction times and high yields, this method facilitates the easy separation of the resultant imines through simple filtration, underscoring water's role as a non-toxic, safe, and cost-effective solvent for such chemical reactions.

A publication in Green Chemistry outlined a water-mediated synthesis of Schiff bases, emphasizing the environmental benefits and simplicity of the process. In a research study published in Green Chemistry Letters and Review, V Koteshwara Rao et. Al [34]. reported the synthesis of Schiff base by stirring 1, 2-diaminobenzene with various aromatic aldehydes in water as solvent. It was reported to be an efficient method that was completed in shorter reaction times (5–22 min) with excellent yields (94–98%). The scheme for this synthesis is shown in Figure 3

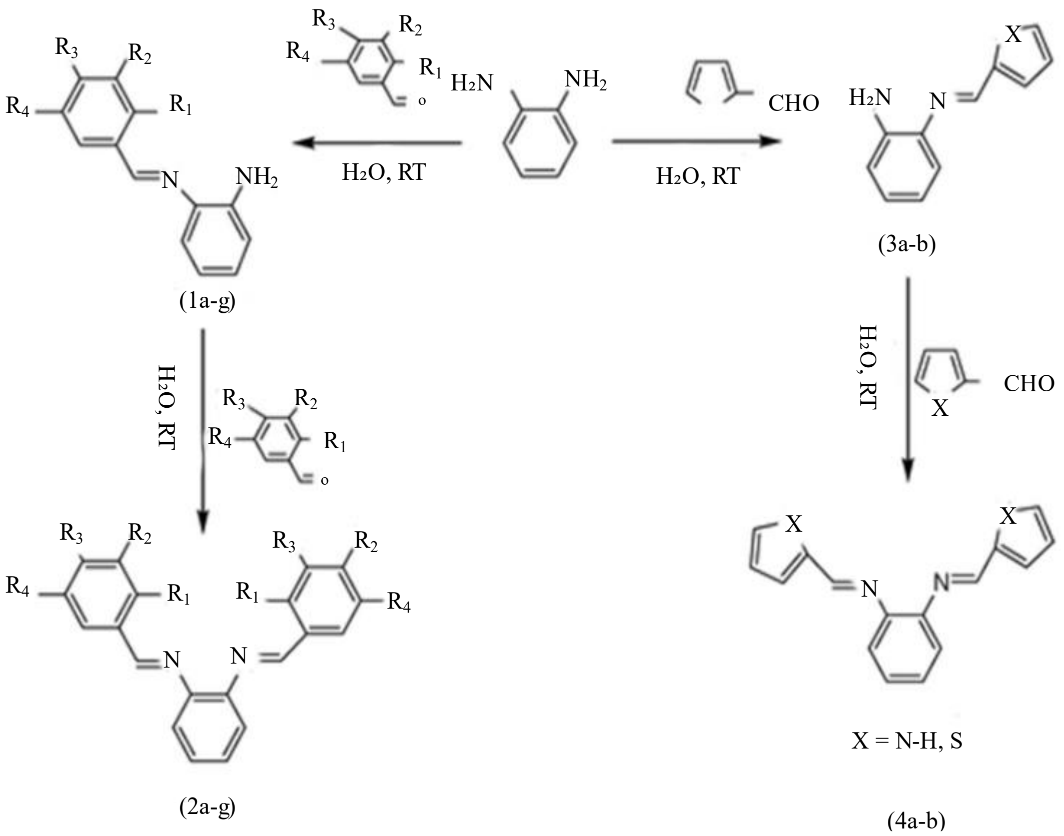


Figure 3. Scheme showing the synthesis of Schiff base in aqueous media.

Smith et al.,in 2019 have demonstrated that water can effectively solubilize both hydrophilic and, with the aid of surfactants or ultra-sonication, hydrophobic substrates for the synthesis of Schiff bases Moreover, water can promote the hydrolysis of imines to aldehydes and amines, which, under equilibrium conditions, can enhance the yields of desired Schiff bases through Le Chatelier's principle according to a study by Jones et al.in 2020.

Supercritical CO_2 as Green Solvent

Carbon dioxide is a component of the atmosphere with a concentration of 412 ppm, steadily increasing from its pre-industrial concentration of ca 280 ppm. It is a product of the combustion of fuel and is emitted in industrial waste streams. Its capture and sequestration for reuse are a major test of the so-called circular economy. It is possible, in principle, to remove carbon dioxide from the atmosphere by so-called Direct Air Capture or from the more concentrated industrial process streams. In either case, the technological and economic challenges are immense. Carbon dioxide currently has applications in the food and drinks industries and enhanced oil recovery. It is readily compressed (>31.0 °C,>72.8 atm) to a supercritical fluid [35]. which finds use in supercritical extraction, such as the removal of caffeine from coffee and dry cleaning. Supercritical CO_2 ($ScCO_2$) is also under active R&D investigation in the production of fine chemicals and pharmaceuticals.$ScCO_2$ both in its liquid and supercritical state, possesses tremendous potential as an eco-friendly medium for sustainable chemical synthesis[36]. In recent decades, there has been a significant surge in research activities, demonstrating the ability of scCO2 to substitute conventional solvents, which may pose environmental risks, across a broad spectrum of processes. On these lines, we hereby analyze the usefulness of $scCO_2$ as a green solvent in the synthesis of Schiff base.

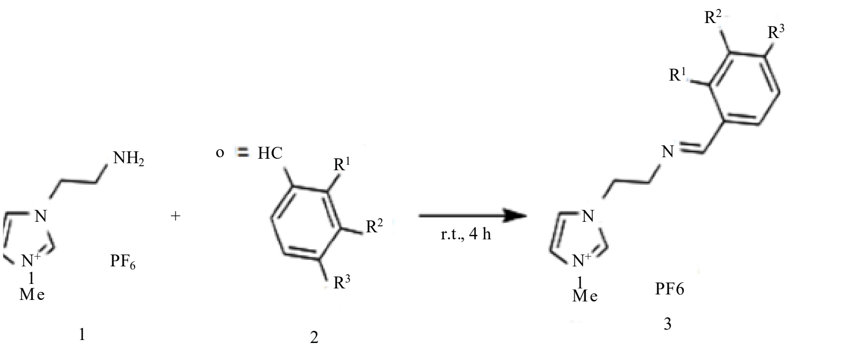
Supercritical carbon dioxide has been explored as an alternative solvent for synthesizing Schiff bases due to its unique properties, including tuneable density, low viscosity, and environmentally friendly nature. Its ability to dissolve a wide range of organic compounds, along with the ease of separation from products, makes it an attractive option for this type of synthesis. Several research studies have investigated the use of $scCO_2$ as a solvent for Schiff base synthesis. These studies have focused on various aspects, including reaction optimization, catalyst design, and the influence of process parameters such as temperature and pressure on the yield and selectivity of the Schiff base formation. In one such study be by Lee and Park [37]. researchers emphasize the optimization of reaction conditions, such as temperature, pressure, and solvent composition, for efficient Schiff base synthesis in scCO2. The authors investigate the influence of these parameters on the reaction kinetics and product yield. They provide insights into the design of reaction systems using $ScCO_2$ as a solvent for Schiff base formation.

The use of co-solvents or modifiers in conjunction with $ScCO_2$ has also been explored to enhance the solubility and reactivity of reactants. Furthermore, researchers have investigated the potential of using $ScCO_2$ in combination with other techniques, such as ultrasound or microwave irradiation, to accelerate the reaction kinetics and improve the efficiency of Schiff base synthesis. The application of novel catalysts and ligands in ScCO2-based systems has also been investigated to promote the formation of Schiff bases and enhance the reaction rate. A study by Smith et al. explored the application of $ScCO_2$ as a green solvent for Schiff base synthesis. It investigated the effect of process parameters, such as temperature, pressure, and reactant concentrations, on the yield and selectivity of Schiff base formation. The authors highlight the advantages of $ScCO_2$ as an environmentally friendly and efficient solvent in this context. A study by Johnson et al. focussed on the development and characterization of catalysts for promoting Schiff base synthesis in $ScCO_2$. It investigated various catalysts, including transition metal complexes supported catalysts, and assessed their efficiency in terms of reaction rate and selectivity. The authors discussed the potential of $ScCO_2$ as a reaction medium for catalytic Schiff base synthesis.

Ionic Liquid

Ionic liquids (ILs) are salts in the liquid state at room or slightly elevated temperatures. They can be customized to enhance the solubility of reactants and can often be recycled. Their non-volatile nature makes them excellent green solvents for chemical synthesis, including Schiff base formation. ILs have been used in catalysis to stabilize nanoparticles for organic reactions. For example, copper nanoparticles stabilized in an IL medium catalysed the Biginelli reaction, leading to the formation of dihydropyrimidinones, compounds known for their broad biological and therapeutic properties. This illustrates ILs' ability to facilitate multicomponent reactions, offering a cleaner alternative to traditional solvents and catalysts that often require harsh conditions. ILs have also been applied in the transformation of biomass into valuable chemicals.

ILs have been designed for tunability in physical and chemical properties, influencing their role in drug delivery and biotechnology. ILs have been investigated for their biocompatibility and toxicity, offering insights into their potential use in biological applications. Various studies highlight ILs' broad impact, extending from chemical synthesis to addressing ecological challenges. The synthesis of Schiff bases using ionic liquids has been a topic of considerable interest in recent years. Ionic liquids, known for their unique properties such as low volatility, thermal stability, and solvating capabilities, have been employed as solvents or catalysts in the synthesis of Schiff bases, offering environmentally benign alternatives to conventional organic solvents. notable method involves the synthesis of ionic liquid-supported Schiff bases through the condensation of aromatic aldehydes with a specific ionic liquid, eliminating the need for any solvent. This approach signifies the growing trend of employing ionic liquids to enhance the efficiency and eco-friendliness of chemical syntheses. The synthesized ionic liquids in such studies often contain the Schiff base functional group, which is integral to their reactivity and potential applications One notable method involves the synthesis of ionic liquid-supported Schiff bases through the condensation of aromatic aldehydes with a specific ionic liquid, eliminating the need for any solvent[38]As shown in Figure 4 Ionic liquid-supported Schiff bases 3a–i were synthesized by condensation of the ionic liquid 1- (2-aminoethyl)-3-methylimidazolium hexafluorophosphate (1) with aromatic aldehydes 2a–i at room temperature without both catalyst and solvent



2,3	R1	R2	R3
a	H	H	cl
b	cl	H	cl
c	H	H	OMe
d	H	H	NO_2
e	H	NO_2	H
f	oH	H	H
g	H	H	Me
h	H	H	Br
i	H	OMe	OH

Figure 4. Scheme showing the synthesis of ionic liquid supported Schiff base.

The synthesized ionic liquids in such studies often contain the Schiff base functional group, which is integral to their reactivity and potential applications [39]. Sodies, et al., investigates the ultrasound-assisted synthesis of pyridinium Schiff bases in ionic liquids and their anticancer activities, demonstrating the enhancement of activity with longer hydrophobic chains.[40]. These studies underscore the versatility and broad applicability of ionic liquids in facilitating complex chemical syntheses and analyses. In an another study a diverse range of imines were successfully obtained in high yields through the reaction of aldehydes and amines in ionic liquids. These ionic liquids could be recovered and reused for a minimum of five cycles without any decrease in yields, presenting an effective alternative to commonly used solvents such as dichloromethane or diethyl ether for this reaction [41]. These developments point towards the expanding scope of ionic liquids in organic synthesis, especially in the formation of Schiff bases. Their application spans various areas of chemical research and industrial processes, showcasing their potential to enhance reaction efficiencies and selectivity while adhering to principles of green chemistry.

Advantages And Limitations of Green Solvents in The Synthesis Pf Schiff's Base

Advantages: The shift towards green chemistry has significantly emphasized the importance of green solvents in chemical synthesis and processing. Geen solvents present a promising path towards more sustainable and environmentally friendly synthesis due to their low toxicity, biodegradability, and minimal environmental impact and thus offer a sustainable alternative to conventional solvents

Sustainable: Green solvents are derived from renewable resources, reducing dependency on fossil fuels and minimizing carbon footprint. Their use aligns with the principles of sustainable development, aiming to preserve the environment for future generations

Low toxicity: One of the primary benefits of green solvents is their reduced toxicity compared to traditional solvents. This characteristic significantly lowers health risks for researchers and workers in the chemical industry, contributing to safer working conditions.

Biodegradable: Green solvents are designed to be biodegradable, ensuring they break down into harmless products that do not accumulate in the environment. This property significantly mitigates the long-term ecological impact associated with solvent disposal

Energy efficient: The use of green solvents can lead to more energy-efficient processes. Their often-lower boiling points compared to conventional solvents mean that less energy is required for processes such as distillation

Economical: Although the initial cost of some green solvents may be higher, their reusability, coupled with reduced health and environmental cleanup costs, can lead to economic advantages in the long-run.

Limitations: Though green solvents offer significant advantages in terms of safety, environmental impact, and sustainability, their limitations in terms of performance, cost, and compatibility highlight the need for further research and innovation.

Non performance: The efficacy of green solvents can vary widely depending on the application, and in some cases, they may not provide the same solvating power as their traditional counterparts. This limitation can restrict their use in certain chemical reactions and processes.

Non availability: Green solvents can be more expensive and less readily available than conventional solvents. This factor can limit their utility.

Non compatibility: Some green solvents may not be compatible with existing equipment or may require modifications to process conditions, potentially leading to additional costs or technical challenges.

Lack of data: The use of green solvents in organic synthesis is a nascent field and hence there is lack of comprehensive data on the properties, toxicity, and environmental impact of many potential green solvents. This gap necessitates further research in this field.

Regulatory issues: Since regulatory landscape for green solvents is still in evolving phase so it may limit the widespread adoption of green solvent

CONCLUSION

Schiff base synthesis is a cornerstone in organic chemistry, with wide applications ranging from organic synthesis to industrial and medicinal chemistry. The integration of green chemistry principles into Schiff base synthesis represents a commitment to sustainability and environmental friendliness in chemical processes. By using green solvents in the synthesis of Schiff bases the principles of green chemistry can be applied aiming to minimize environmental impact while enhancing efficiency and safety. Green chemistry emphasizes the importance of waste prevention at its source. In Schiff base synthesis, this is achieved through the use of solvent-free reactions or green solvents, significantly reducing the generation of hazardous waste. Further, traditional solvent-based reactions pose risks due to toxicity and volatility. The use of green solvents, such as water, ionic liquids, or supercritical fluids, in Schiff base synthesis minimizes these risks. Ionic liquids, in particular, offer advantages due to their low volatility and reusability, aligning with the principles of green chemistry

The integration of green chemistry principles into Schiff base synthesis represents a pivotal shift towards more sustainable chemical processes. By prioritizing waste reduction, safety, energy efficiency, and the use of renewable resources, chemists can minimize environmental impact while advancing the frontiers of science. As research progresses, the continued refinement of methods and materials promises to further align Schiff base synthesis with the ideals of green chemistry, benefiting both the environment and society at large

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